Cell Stem Cell
Previews

Short-Circuiting Epiblast Development

Kevin Eggan[1,2,3,*]
[1]The Stowers Medical Institute
[2]The Harvard Stem Cell Institute
[3]Department of Molecular and Cellular Biology
Harvard University, 7 Divinity Avenue, Cambridge, MA 02138, USA
*Correspondence: eggan@mcb.harvard.edu
DOI 10.1016/j.stem.2007.07.018

Although human and mouse embryonic stem cells share many characteristics, their behaviors are not identical. Two recent papers describe the derivation of stem cell lines from mouse epiblast that may provide an explanation for the unique character of human embryonic stem cells.

The capacity of embryonic stem cells to self-renew indefinitely while maintaining their potential to differentiate into any cell in the embryo has been a valuable tool for mouse geneticists for decades (Bradley et al., 1984). The subsequent derivation of these cells in primates (Thomson et al., 1998) has revolutionized the way we think about both transplantation medicine and drug discovery. However, despite the time that has passed since embryonic stem cells were first derived, many questions concerning the nature of these cells persist. What counterpart, if any, do these cells have within the embryo in vivo? What is the explanation for the differences in behavior between mouse embryonic stem cells and their human counterparts? Why has it been so difficult to derive embryonic stem cell lines from other species of animals, despite the clear benefits that the application of such cells would bring?

Two recent papers published in the journal *Nature*, one from the McKay lab (Tesar et al., 2007) and the other by Vallier and colleagues (Brons et al., 2007), shed light on these interesting questions. In both reports, the authors describe the derivation of self-renewing, pluripotent populations of cells from the epiblast of postimplantation mouse embryos, a later developmental stage than the blastocysts used previously. These cells are similar to other mouse embryonic stem cell lines in that they can form embryoid bodies in culture and teratomas in nude mice, and within these masses, differentiated cells from each of the three embryonic germ layers are generated.

However, these "epiblast stem cells," as the authors dubbed them, seem to be distinct from mouse embryonic stem cells derived from blastocyst stage embryos in several ways. Of particular note, many of the altered traits observed in epiblast stem cells are consistent with the salient characteristics of human embryonic stem cells. These new pluripotent mouse cell lines appear to have gene expression patterns distinct from blastocyst-derived embryonic stem cells; require Activin, rather than LIF signaling for self-renewal; and grow in tight epithelial structures reminiscent of human embryonic stem cells.

Because of their derivation from postimplantation epiblast, and as Activin/Nodal signaling is important for maintenance of both the mouse epiblast in vivo (Camus et al., 2006) and human embryonic stem cells in vitro (James et al., 2005), it is tempting to speculate, as the authors do, that the derivation of these new mouse stem cell lines indicates that human embryonic stem cells might represent a short circuiting of human epiblast development and the capture of an in vitro counterpart to these cells. Consistent with this notion, when the authors transplanted these cells into preimplantation blastocysts they possessed very limited or no ability to contribute to the resulting embryo.

Thus far, most mammalian species have been refractory to the derivation of embryonic stem cell lines of the type cultured from mouse blastocysts. In their study, Brons and colleagues also demonstrate that these epiblast stem cells can be derived from rat embryos, a model organism from which there have been numerous but unsuccessful attempts to derive embryonic stem cell lines. The generation of these similar cell lines from mouse, human, and rat suggests that encouraging the self-renewal of epiblast cells may be a more applicable Rosetta stone for translating the derivation of pluripotent stem cells into other species. However, if these cells cannot be forced to contribute in a meaningful way to chimeric offspring, as the authors found for their mouse epiblast stem cells, the utility of the orthologous cells will be greatly limited.

Although these studies are significant, they leave several questions unaddressed and ripe for further investigation. In their studies, Tesar and Brons were only able to isolate these cells from postimplantation embryos and not blastocyst stage embryos. This would be consistent with an epiblast origin and nature for these cells. However, why then can primate and human embryonic stem cells be derived from blastocyst stage embryos and why do primate, but not murine, blastocyst-derived cells have similar characteristics to their postimplantation-derived mouse counterparts? Is it that cells within the inner cell mass of human blastocysts are beginning to adopt epiblast characteristics and it is these cells that become human embryonic stem cells? If so, would prolonging the in vitro culture of human blastocysts prior to derivation increase the efficiency of human embryonic stem cell derivation? Furthermore, would these later cell lines have the same characteristics found in existing human embryonic stem cell lines?

A perhaps more perplexing question is, if these new mouse stem cell lines and human embryonic stem cells represent a self-renewing population of definitive embryonic epiblast cells, why then do both of these populations retain the capacity to differentiate into extraembryonic trophectoderm and primitive endoderm? Lineage tracing experiments in mice would suggest that the epiblast has extremely limited capacity, if any, to differentiate into these cells types (Gardner and Rossant, 1979; Lawson et al., 1991), while the cultured epiblast stem cell lines seem to adopt these cell fates readily. Could it be that without the constraints of their in vivo environment this wider developmental potential for epiblast cells is revealed? Does prolonged in vitro culture somehow lead to an expansion of developmental potential, or is there some other explanation for the remarkable potential of both these epiblast-derived mouse cells and human embryonic stem cells?

Regardless of the answers to these questions, the work of Brons and Tesar and their colleagues has provided exciting new information concerning the nature and origins of both mouse and human embryonic stem cells, suggesting a potential explanation for their distinct biology.

REFERENCES

Bradley, A., Evans, M., Kaufman, M.H., and Robertson, E. (1984). Nature *309*, 255–256.

Brons, I.G., Smithers, L.E., Trotter, M.W., Rugg-Gunn, P., Sun, B., Chuva de Sousa Lopes, S.M., Howlett, S.K., Clarkson, A., Ahrlund-Richter, L., Pedersen, R.A., and Vallier, L. (2007). Nature *448*, 191–195.

Camus, A., Perea-Gomez, A., Moreau, A., and Collignon, J. (2006). Dev. Biol. *295*, 743–755.

Gardner, R.L., and Rossant, J. (1979). J. Embryol. Exp. Morphol. *52*, 141–152.

James, D., Levine, A.J., Besser, D., and Hemmati-Brivanlou, A. (2005). Development *132*, 1273–1282.

Lawson, K.A., Meneses, J.J., and Pedersen, R.A. (1991). Development *113*, 891–911.

Tesar, P.J., Chenoweth, J.G., Brook, F.A., Davies, T.J., Evans, E.P., Mack, D.L., Gardner, R.L., and McKay, R.D. (2007). Nature *448*, 196–199.

Thomson, J.A., Itskovitz-Eldor, J., Shapiro, S.S., Waknitz, M.A., Swiergiel, J.J., Marshall, V.S., and Jones, J.M. (1998). Science *282*, 1145–1147. Erratum: (1998). Science *282*, 1827.

Stem Cells Remember Their Grade

Cristina Lo Celso[1] and David T. Scadden[1,*]
[1]Center for Regenerative Medicine, Massachusetts General Hospital, Harvard Stem Cell Institute, Boston, MA 02114, USA
*Correspondence: scadden.david@mgh.harvard.edu
DOI 10.1016/j.stem.2007.07.011

The stem cell state is understood based on what cells do in performance assays, crude measures of a highly refined state. In this issue of *Cell Stem Cell*, Dykstra et al. (2007) reveal stem cell gradation and the extent to which that gradation is retained in stem cell daughters of hematopoietic stem cells.

Adult stem cells are known by what they do. We can see them through their power to create multilineage offspring that reconstitute a tissue. This trait allowed Till and McCullough to provide the experimental proof that stem cells do indeed exist (Till and McCullough, 1961), but it remains a vexingly difficult way to study the cells in detail. If we are forced to use a retrospective analysis to define stem cells, we are never able to know them as they are, but only as what they have become. In hematology, this has led to a highly productive effort to prospectively define subsets of bone marrow cells by immunophenotype that could be then tested for function. Iterative analysis had led to defined subsets enriched for reconstituting bone marrow long term: the functional signature of a hematopoietic stem cell (Adolfsson et al., 2001; Christensen and Weissman, 2001; Goodell et al., 1996; Kiel et al., 2005; Li and Johnson, 1995; Osawa et al., 1996). This process of finer and finer parsing of function is simple in concept but agonizingly slow in conduct, and such studies are population based. They have yielded stem cells on a single-cell basis, but not uniformly (Camargo et al., 2006; Osawa et al., 1996).

That stem cells are rarely uniformly capable of reconstitution on a single-cell level has raised several interesting possibilities. Do we simply not yet have the precise set of signature markers for stem cells? Might we be disrupting some of the fundamental features of the cells by the means we use to isolate them? Or, most intriguingly, might these cells be a fundamentally unstable cell type with varying, graded functions: a core tradeoff for having the capabilities they do. The Eaves lab has tried to address this with studies that distill subpopulations down to their single-cell constituents and then looking back on what they have wrought (Dykstra et al., 2007). It was a Herculean undertaking, evaluating over 350 single-cell transplantations in mice for over 4 months each.

So just how uniform are stem cells? First, the caveat: the cells were isolated based on a method that is somewhat unconventional. Lineage marker negative, CD45 mid, rhodamine low, and Hoechst 33342 excluding